Necesidades insatisfechas en casos de hemofilia A severa sin inhibidores en Argentina: un estudio de corte transversal.

Unmet needs for severe hemophilia A cases without inhibitors in Argentina: a cross-sectional study.

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Abstract

Introduction. Hemophilia A (HA) is a rare inherited disorder due to a gene mutation encoding the clotting factor VIII. For Argentina, a prevalence of 10.4 per 100,000 males was reported in 2021. Through real-world data, we aim to describe the sociodemographic and clinical characteristics, outcomes and healthcare resources utilization of Argentinian HA individuals without inhibitors.

Materials and methods. A cross-sectional study was carried out based on data collected through a structured 55 multiple-choice and gap-filling questionnaire from August to September 2020 and from March to April 2021. Hematologists were surveyed about HA cases in their practice, providing information on sociodemographic and clinical characteristics, outcomes, and healthcare resources utilization.

Results. We gathered data from 20 hematologists, who provided information on 97 HA cases. Out of the 20 hematologists, 35% have been practicing the specialty for 6 to 10 years, 20% for 11 to 15 years, 10% for 16 to 20 years, and 35% for more than 20 years. Regarding the cases, in our primarily male sample (97.9%), we found a mean age of 39.6 years (±14.3) and mean weight of 73.3 kg (±13.4). Of the total cases, 19.6% had mild disease, 23.7% had moderate disease, and 56.7% had severe disease. Over half of the cases were receiving prophylaxis (59.8%; primary 27.6%, secondary 53.4%, and tertiary 19%), and 40.2% were on-demand therapy; adherence was 50-80% and >80% in 36.2% and 55.2% of cases, respectively. Inadequate FVIII prophylaxis was not seen in our sample, yet 24.7% of cases reported a switch in treatment; of them, 83.3% corresponded to

cases with severe disease. The overall average annualized bleeding rate (ABR) was 4.7 (±8.2) (mild: 2.8 (±6.4), moderate: 3.2 (±6.9), and severe: 6 (±9.2)). Mobility restrictions were seen in 60% of cases with severe disease, and in 21.7% and 21.1% of cases with moderate and mild disease, respectively. Further, 38.2% of cases with a severe disease were ineligible for surgery, 52.2% of those had a moderate disease, and 15.8% of those had a mild disease. High-dose prophylaxis was also more frequent in cases with a severe disease (53.7% vs. mild: 28.6% and moderate: 10.0%).

Discussion. Over half of the cases had a severe HA disease; despite appropriate doses and application intervals, they showed a higher ABR, mobility restriction, and consumption of FVIII. Our study underscores the unmet medical needs for Argentinian HA individuals without inhibitors; addressing these is essential to optimize their care.

Resumen

Introducción. La hemofilia A (HA) es un trastorno hereditario poco frecuente secundario a una mutación en el gen que codifica el factor VIII de la coagulación. Para Argentina, se reportó una prevalencia de 10.4 por 100,000 hombres en 2021. A través de evidencia del mundo real, nuestro objetivo es describir las características sociodemográficas y clínicas, los resultados y la utilización de recursos sanitarios de individuos argentinos con HA sin inhibidores.

Materiales y métodos. Se realizó un estudio de corte transversal basado en datos recolectados a partir de un cuestionario de 55 preguntas de opción múltiple de agosto a septiembre de 2020 y de marzo a abril de 2021. Le preguntamos a los hematólogos acerca de sus casos, dando información acerca de las características sociodemográficas y clínicas, los resultados y la utilización de recursos sanitarios.

Resultados. Reunimos datos de 20 hematólogos quienes brindaron información de 97 individuos con HA. De los 20 hematólogos, el 35% reportó de 6 a 10 años de ejercicio de la especialidad, el 20% de 11 a 15 años, el 10% de 16 a 20 años y el 35% más de 20 años. Respecto a los casos, en nuestra muestra mayoritariamente masculina (97.9%), encontramos una media de edad de 39.6 años (±14.3) y de peso de 73.3 kg (±13.4). Del total de casos, 19.6% tenía una enfermedad leve, 23.7% tenía una enfermedad moderada

y 56.7% una enfermedad severa. Más de la mitad recibían profilaxis (59.8 %; primaria 27.6%, secundaria 53.4% y terciaria 19%) y 40.2% recibían tratamiento a demanda; la adherencia fue del 50-80% y >80% en el 36.2% y el 55.2% de los casos, respectivamente. No se observó profilaxis inadecuada con FVIII, sin embargo, 24.7% de los casos reportaron un cambio de tratamiento; de ellos, 83.3% padecían HA severa. La tasa de sangrado promedio anual fue de 4.7 (±8.2) en general (leve: 2.8 (±6.4), moderada: 3.2 (±6.9) y severa: 6 (±9.2)). Hubo restricciones de movilidad en 60% de los casos con una enfermedad severa, y en 21.7% y 21.1% de aquéllos con enfermedad moderada y leve, respectivamente. Adicionalmente, 38.2% de los casos con una enfermedad severa, 52.2% de aquéllos con una enfermedad moderada y 15.8% de aquéllos con una enfermedad leve no fueron elegibles para cirugía. La profilaxis a altas dosis también fue más frecuente en casos con una enfermedad severa (53.7% vs. leve: 28.6% y moderada: 10.0%).

Discusión. Más de la mitad de los casos tenía una enfermedad HA grave; a pesar de las dosis e intervalos de aplicación del tratamiento correctos, presentaron una tasa de sangrado promedio anual más alta, mayor frecuencia de restricción de movilidad y consumo de FVIII. Nuestro estudio resalta necesidades médicas insatisfechas para individuos argentinos con HA sin inhibidores; el abordaje de estas necesidades es esencial para optimizar su cuidado.

Introduction

Hemophilia A (HA) is a rare X-linked recessive disorder arising from a mutation of the gene encoding the blood clotting protein factor VIII[1]. For Argentina, the 2021 Annual Global Survey by the World Federation of Hemophilia (WFH) reported a total of 2,366 male HA cases and a prevalence of 10.4 per 100,000 males: Also, from a total of 2448 cases that included female HA patients in Argentina, the majority had a severe (55%) disease followed by mild (23%) and moderate (13%) phenotypes; severe disease was defined as having less than 1% of the normal amount of clotting factor, moderate disease as having between 1-5% of the normal amount of clotting factor, and mild disease as having >5-40% of the normal amount of clotting factor[2].

Prophylaxis must be started even before symptoms onset; if the joint damage is established, it cannot

be reversed, thus, reducing bleeding and long-term complications[3]. The choice of specific prophylactic therapy is to maintain factor levels above 1 UI/dL (1%) outside the range of severe hemophilia; however, recent recommendations state that the target is meant to be made on a case-by-case basis, highlighting those levels of 1-3 IU/dL (1%-3%) might be insufficient and proposing targets of up to 15 IU/dL (15%) for preventing spontaneous bleeding episodes[4,5]. Factor VIII clotting factor concentrates (CFCs) may be plasma-derived or recombinant products and are divided into SHL (standard half-life) and EHL (extended half-life). Additionally, since its approval in 2017, therapy with the recombinant humanized bispecific monoclonal antibody emicizumab (Hemlibra®), which mimics FVIII and has the capacity to bind simultaneously to activated factor IX and factor X, may also be considered as an alternative to factor replacement[6].

The 2021 Guideline for managing congenital hemophilia of the Argentinian Hemophilia Foundation recommends life-long prophylactic treatment for HA with a severe phenotype (i.e., recurrent hemarthrosis). SHL CFCs 3 times a week or EHL CFCs 2 times a week is indicated in addition to pharmacokinetics monitoring to optimize/adjust dosing. Emicizumab is also recommended, but only for HA cases, weekly or every other week. Overall, SHL and EHL CFCs prophylaxis should be administered intravenous (IV). A weekly follow-up must be guaranteed, and the annualized bleeding rate (ABR) must be assessed to adjust the treatment according to the patient's clinical response, physical activity, and adherence[7].

Despite the promising long-term clinical outcomes, there are still some unmet needs for patients both on prophylaxis and on-demand treatment, such as decreased mental health[8], impaired mobility, and occasional pain or discomfort[9]. In Argentina, there is information on clinical outcomes in HA individuals with inhibitors reporting a mean overall ABR of 7.68 (±8.18), although the information regarding cases without inhibitors is relatively scarce[10]. In mid-2016, a survey among specialists in Latin America (including Argentina) reported unmet needs such as the importance of a national registry, the absence of a multi-stakeholder decision-making process, the supply barriers of CFCs in some countries,

restrictions on the use of prophylaxis (e.g., due to the absence of insurance coverage in Argentina for adults), and the lack of clinical- and health-services research[11].

Ahead of the complexity of this condition in a clinical and socio-cultural context and the inherent complications, we find in the effects of pharmacological treatment a conceptual bridge to the understanding of the multifactorial burden of the disease. Taking this, together with the fact that only a few studies describe the current state of HA not only in Argentina but also in Latin America[12] and the lack of centralized HA registries[5], motivates the purpose of this study to reduce this knowledge gap by attempting to characterize through real-world data the unmet needs and demands in Argentinian HA individuals without inhibitors.

Materials and methods

This is a cross-sectional study based on information collected through the application of a questionnaire in the form of a patient diary. Twenty hematologists were invited and accepted to participate in the gathering of data of a convenience sampling of adult individuals (≥ 18 years) with a confirmed diagnosis of HA without inhibitors. The hematologists were randomly selected from a physician's database affiliated with the clinical research organization IQVIA. The selection criteria were based on their involvement with hemophilia reference centers, their experience in treating patients with hemophilia A without inhibitors and the routinely documentation of their patients' clinical data, including prescription records, as an integral part of their follow-up practices. Data were collected through phone and/or web-based interviews following a structured 55 multiple-choice and gap-filling questionnaire and registered anonymously in a centralized database during August-September 2020 and March-April 2021. Participating hematologists were surveyed about HA cases in their practice; data were collected only one time for each case providing information on sociodemographic characteristics, and clinical data. Health Care Resource Utilization (HCRU) information was also collected. Adequate prophylaxis was defined as the use of either high dose prophylaxis (25-40 IU FVIII/kg every 2 days), intermediate dose prophylaxis (15-25 IU FVIII/kg 3 days per

week) or low-dose prophylaxis (10-15 IU FVIII/kg 2-3 days per week)[5].

Due to the descriptive observational nature of our study, no statistical hypothesis testing was intended. All statistical analyses were performed using R language and environment for statistical computing. The study protocol was carried out following the ethical standards of the 1975 Declaration of Helsinki. Written consent from the individuals was not obtained as the study gathered information from hematologists rather than directly from the individuals themselves. Hematologists were informed of the study's purpose and the anonymity of their HA cases' data and were asked to consent to participate.

Results
Sociodemographic and clinical characteristics

Out of the 20 hematologists, seven (35%) have been practicing the specialty for 6 to 10 years, 4 (20%) for 11 to 15 years, one (5%) for 16 to 20 years, and seven (35%) for more than 20 years. Information provided on 97 HA cases was included in the analysis. In our primarily male sample (n=95, 97.9%), we found a mean age of 39.6 years (±14.3) within a range of 18 to 73 years, and more than half belonged to the 18 to 39 age group (n=57, 58.8%). The mean weight was 73.3 kg (±13.4) within a range of 40 to 128 kg, and almost two-thirds of the participants (n=61, 62.9%) reported doing physical activity regularly: 4-7 times per week (n=5), 1-3 times per week (n=38), or every two weeks (n=15).

Furthermore, a minority reported having hepatitis C (n=11, 11.3%), hepatitis B (n=5, 5.2%), HIV (n=2, 2.1%) or another unspecified liver disease (n=1, 1%) within the cases comorbidities. Regarding the insurance regimes, for 42 (43.3%) cases it was reported belonging to an *OOSS* (in Spanish, *Obras Sociales*), for 28 (28.9%) to the *PAMI* (in Spanish, *Programa de Atención Médico Integral*), for 18 (18.6%) to public coverage, and for 9 (9.3%) to prepaid coverage. Additionally, table 1 compares the summary statistics according to the severity of the disease.

Table 1. Sociodemographic and clinical characteristics per severity of HA.

	Mild (n=19, 19.6%)	Moderate (n=23, 23.7%)	Severe (n=55, 56.7%)	Total (n=97)
Age, mean (SD)	42.4 (13.5)	50.6 (16.4)	34.1 (10.5)	39.6 (14.3)
Age group, n (%)				
18 – 39	9 (47.4%)	6 (26.1%)	42 (76.4%)	57 (58.8%)
40 – 59	7 (36.8%)	7 (30.4%)	11 (20.0%)	25 (25.8%)
60 – 69	2 (10.5%)	9 (39.1%)	2 (3.6%)	13 (13.4%)
≥70	1 (5.3%)	1 (4.3%)	0 (0.0%)	2 (2.1%)
Weight, mean (SD)	76.4 (9.9)	67.9 (12.7)	74.5 (14.2)	73.3 (13.4)
Physical activity, n (%)	12 (63.2%)	22 (95.7%)	27 (49.1%)	61 (62.9%)
1-3 times per week	5 (41.7%)	16 (72.7%)	17 (63%)	38 (62.3%)
4-7 times per week	4 (33.3%)	0	1 (3.7%)	5 (8.2%)
Every 15 days	0	6 (27.3%)	9 (33.3%)	15 (24.6%)
Missing	3 (25%)	0	0	3 (4.9%)
Healthcare coverage, n (%)				
OOSS *Nacionales*	4 (21.1%)	3 (13.0%)	15 (27.3%)	22 (22.7%)
OOSS *Provinciales*	1 (5.3%)	0 (0.0%)	12 (21.8%)	13 (13.4%)
PAMI	10 (52.6%)	12 (52.2%)	6 (10.9%)	28 (28.9%)
Public	0 (0.0%)	6 (26.1%)	12 (21.8%)	18 (18.6%)
Prepaid	1 (5.3%)	1 (4.3%)	7 (12.7%)	9 (9.3%)
Unknown	3 (15.8%)	1 (4.3%)	3 (5.5%)	7 (7.2%)
Treatment, n (%)				
Prophylaxis	7 (36.8%)	10 (43.5%)	41 (74.5%)	58 (59.8%)
On-demand	12 (62.2%)	13 (56.5%)	14 (25.5%)	39 (40.2%)

Treatment and HCRU

Regarding the treatments, prophylaxis was more frequent in those with severe disease than those with moderate and mild disease (74.5% vs. 43.5 and 36.8%). Among those on prophylaxis, 31 (53.4%) received secondary prophylaxis, 16 (27.6%) primary prophylaxis, and 11 (19%) tertiary prophylaxis; further, 49 (84.5%) of them received a standard regimen, and 9 (15.5%) of them were on a "case by case" approach (i.e., if individuals continue to experience bleeds, their prophylaxis regimen was escalated (in dose/frequency or both) to prevent bleeding). Recombinant products were the most common (n=35, 55.2%), followed by plasma-derived products (n=24, 41.4%) and emicizumab (n=2, 3.4%). When comparing cases on prophylaxis to those on demand, they were younger (36.6 (±15.4) vs. 44.1 (±11.5)), more active (67.2 vs. 56.4%), and had a lower weight (71.1 kg (±12.2) vs. 75.36 kg (±14.7)).

Inadequate FVIII prophylaxis was not seen in our sample; yet, high-dose prophylaxis, intermediate dose prophylaxis, and low-dose prophylaxis were noticed on 25 (43.1%), 26 (44.8%), and 3 (5.2%) of the cases, respectively; dose data were missing for two cases. Further, the two (3.4%) cases on emicizumab had a dose of 2 mg/kg. FVIII prophylaxis mean dose per application was 29 (±7.2) UI/kg in ranges from 10 to 50 UI/kg; additionally, the most common frequency of administration regimen was 3 times per week (n=49, 84.5%) followed by twice (n=5, 8.6%) and once (n=3, 5.2%) per week; frequency data were missing for one case (n=1, 1.7%). Also, for 24 cases (24.7%) it was reported a switch in treatment; of them, 20 cases corresponded a severe disease, and the most common switch was from a plasma-derived to recombinant products (n=21), other types of switches such as from a plasma-derived to other plasma-derived product, from a recombinant to a plasma-derived product, and from a recombinant to other recombinant product were reported each in one case.

When considering pre-prophylaxis treatments, 9 (9.3%) and 16 (16.5%) cases received plasma-derived or recombinant factor VIII, respectively. Also, adherence (subjectively evaluated by the treating hematologist) of cases on prophylaxis was greater than 80% (n=32, 55.2%) in over half of them, followed by 50-80% (n=21, 36.2%) and less than 50% (n=5, 8.6%). On-demand therapy was more frequent in cases with mild and moderate disease than in those with severe (63.2 and 56.5% vs. 25.5%). Detailed information of prophylaxis and adherence according to the severity of the disease is shown in supplementary table S1.

On the other hand, regarding HCRU, for 35 (36.1%) cases it was reported having a monthly outpatient consultation, 30 (30.9%) a quarterly consultation, 18 (18.6%) a biannual consultation, 11 (11.3%) a bimonthly consultation and three cases sporadically whenever needed. The most common methods for evaluating joints were ultrasound alone (n=47, 48.5%) and in combination with MRI (n=32, 33%), followed by MRI alone (n=11, 11.3%).

When asking about the cause of consultations, they reported that for 42 cases it was a routine follow-up consultation; other causes include those related to prophylaxis application (n=29), laboratory test (n=25), prescription pick up (n=19), bleeding episodes (n=19), and physiotherapy (n=9). Conversely, only 18 (18.6%) reported being hospitalized once in the previous 12 months, with an average length of stay of 6 (±3.7) days and ranges of 2 to 15 days. Supplementary table S2 shows HCRU per severity of the disease and per type of treatment.

Outcomes

In the final part of the questionnaire, hematologists were asked about outcomes. For 76 (78.4%) cases it was reported having at least one bleeding episode in the past year; thus, over half of them (n=39, 51.3%) had only one episode, followed by two (n=12, 15.8%), three (n=10, 13.2%), four (n=4, 5.3%), 24 (n=3, 3.9%), and 30 episodes (n=2, 2,6); also, 13, 14, 15, 28, and 40 episodes were reported each in one case (n=1, 1.3%). The overall ABR was 4.7 (±8.2); it was higher for cases receiving on-demand treatment than those on prophylaxis (7.4 (±10.2) vs. 2.7 (±5.9)). Further, for cases with a mild disease was 2.8 (±6.4), for those with a moderate disease was 3.2 (±6.9), and for those with a severe was 6 (±9.2). The ABR range was of 1 to 40 episodes.

Isolated external and internal bleeding were the more common types of bleeding (n=28 (36.8%) and n=27 (35.5%), followed by the concomitancy of both (n=21, 27.6%). Similarly, traumatic bleedings were more frequent than spontaneous bleedings (n=32 (42.1%) vs. n=26 (34.2%)), being concomitant in 18 (23.7%) cases. In addition, it was reported joint

bleeding for 42 (55.3%) cases, muscular bleeding for 12 (15.8%), and both for 17 (22.4%) cases. Finally, for 20 (26.3%) cases it was reported suffering from more than two bleeds in the same joint in the past 12 months.

Concerning additional outcomes, 61 (62.9%) were considered eligible for a surgical procedure. Mobility was reported as unrestricted in 55 (56.7%) cases, though exhibited mild (no support but with limitations), moderate (use of supports such as a walker), and severe (unable to move on their own) impairment in 30 (30.9%), 11 (11.3%), and 1 (1%) of cases, respectively. Also, 69 (71.1%) cases were reported as employed and active, 15 (15.5%) were retired, and 9 (9.3%) were unemployed or inactive. Figures 1-4 present a complementary illustration of the outcomes per severity of the disease and per type of treatment.

Figure 1. Bleeding episodes in the last 12 months per severity of the disease and type of treatment.
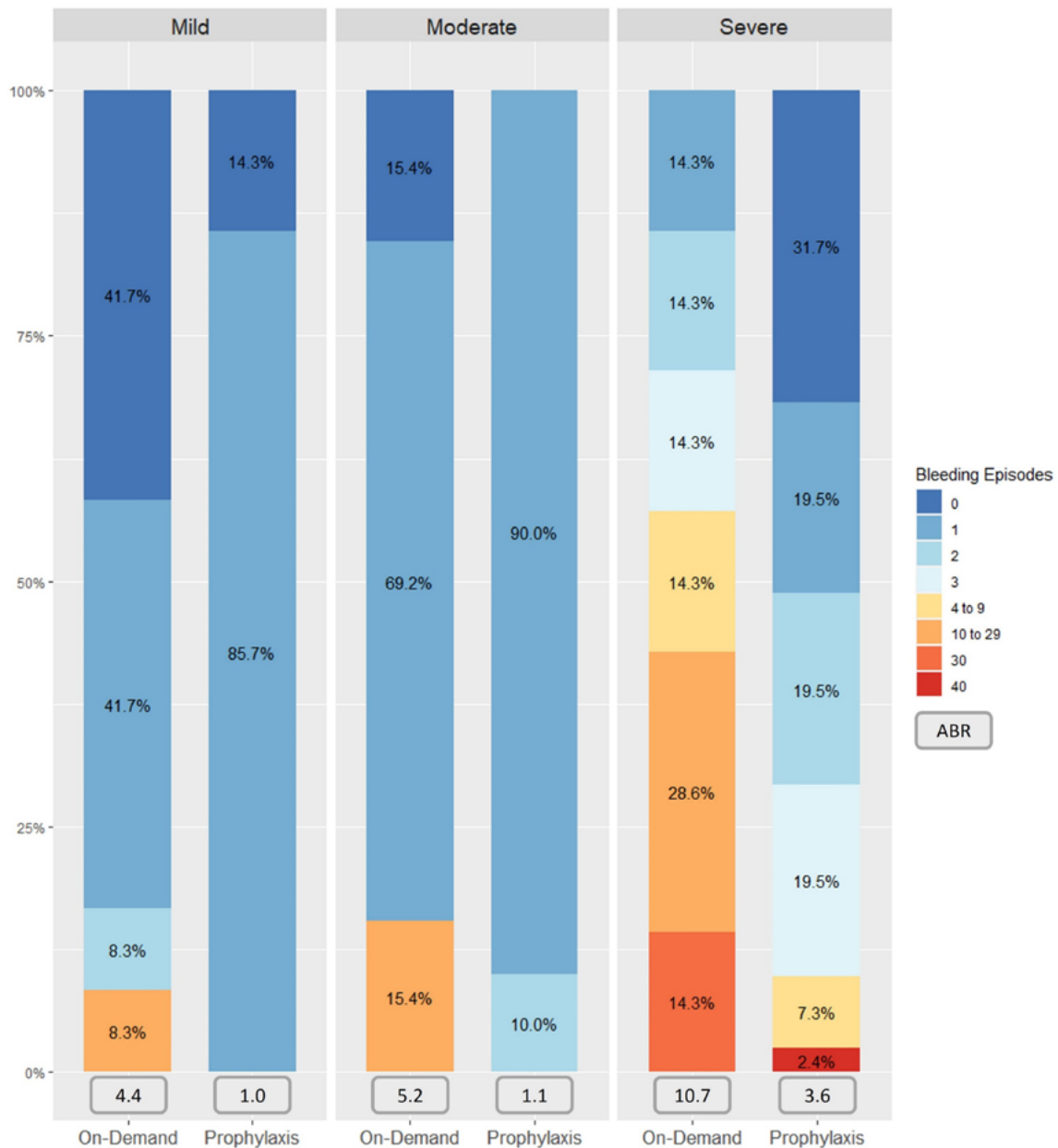
ABR: Annualized Bleeding Rate.

Figure 2. Mobility restriction per severity of the disease and type of treatment.
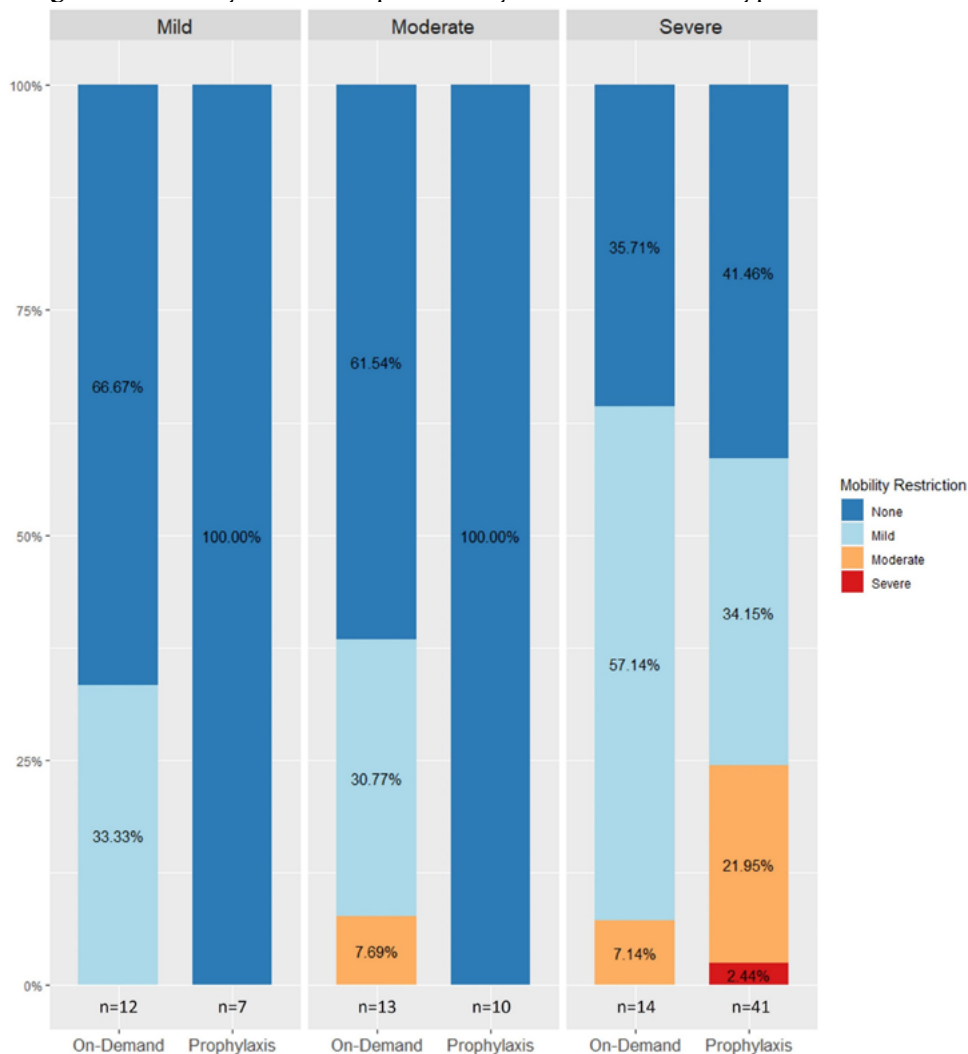
Discussion

This study set out to describe, through real-world data collected in patient diaries, the sociodemographic and clinical characteristics, outcomes and health resource utilization of Argentinian HA individuals without inhibitors. The overall average ABR was 4.7 (±8.2) and it was higher for individuals receiving on-demand treatment than those on prophylaxis (7.4 (±10.2) vs. 2.7 (±5.9)). For severe cases it was slightly higher when compared to those with a moderate or mild disease disregard the type of treatment they received (on-demand: 10.7 (±11.2) vs. 4.4 (±8.6) and 5.2 (±9.3); prophylaxis: 3.6 (±7.2) vs. 1.1 (±0.3) and 1.0 (±0.0)).

Higher ABR, like ours have been observed outside of clinical trials[13,14], suggesting a logical difference between both settings, these results corroborate the findings of a great differences not only between treatment regimens (on-demand vs. prophylaxis) but also between trials and real-world studies. Kruse-Jarres et al. report that prophylactic treatment was also associated with lower median annualized bleeding rates vs. on-demand (1.9 vs. 31.1)[6]. Among individuals on prophylaxis, just 14.3% of cases with a mild disease and 31.7% of those with a severe disease presented 0 bleeding episodes in the last year; however, we found no cases of individuals on prophylaxis and a moderate disease having 0 bleeding episodes in the last year. A possible explanation for this, could be the predominance of prophylaxis with a recombinant FVIII in mild and severe disease compared to moderate (56.1% and 100% vs. 20%).

Figure 3. ≥ 2 bleeding episodes in the same joint in the last 12 months per severity of the disease and type of treatment.
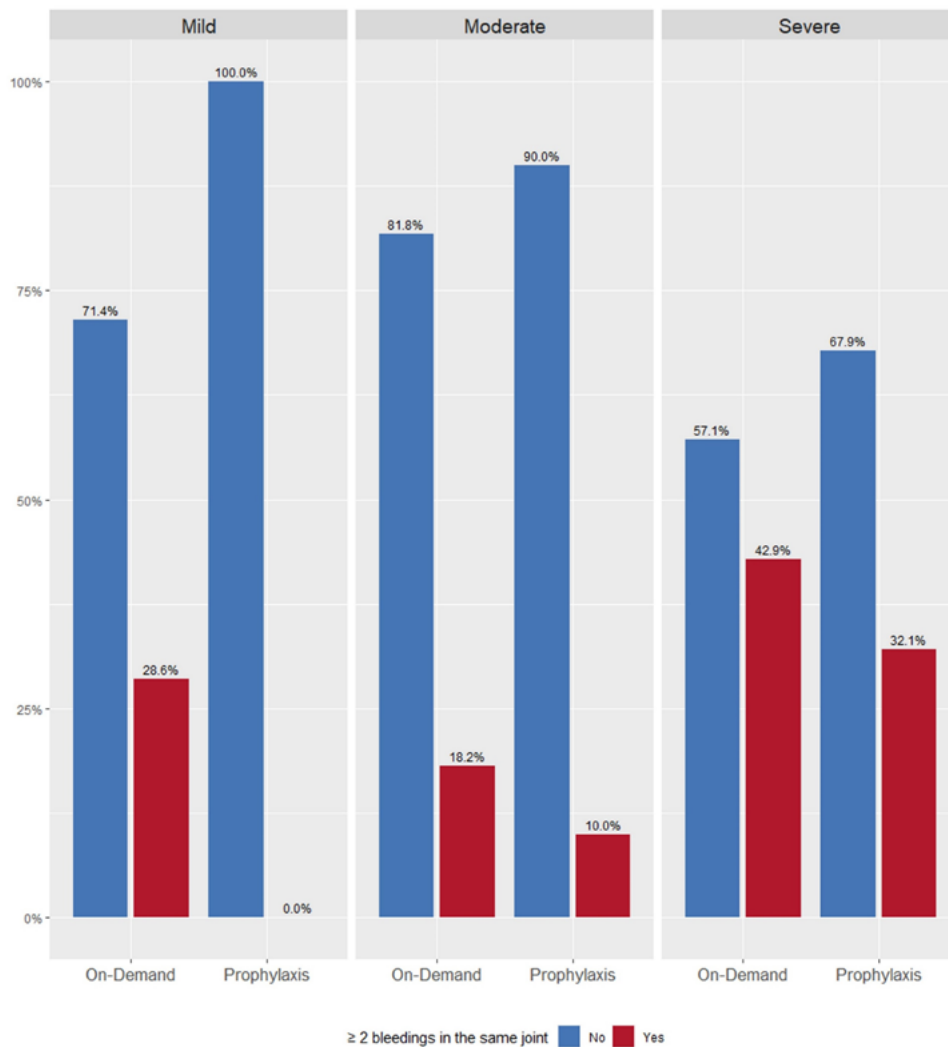

There were 21 missing data for this variable (mild=6, moderate=2, and severe=21); therefore, absolute frequencies may differ from the ones reported for the entire sample.

As expected, secondary and high-intensity prophylaxis were more frequent in severe diseases (65.9% and 53.7%) and less in moderate diseases. On the other hand, individuals who were on-demand therapy showed a higher frequency of bleeding events which conditioned a higher consumption of FVIII; thus, this could justify prophylaxis with much better clinical outcomes[15].

The great majority of mild, moderate, and severe individuals on prophylaxis received three applications per week, and the mean dose per application was moderately similar for all of them; however, dosing frequency ranges were wider for severe and mild individuals, and narrower for moderate individuals.

This is related to the fact that 84.5% of individuals received a standard prophylaxis regimen. Finally, there were higher rates of a switch of treatments for severe individuals, the most common cause was due to medical decisions and product bidding, in contrast to a lower impact of the insurer's decision.

Similarly, the absence of mobility restriction was less frequent in severe diseases (41.5% on prophylaxis and 35.71 receiving on-demand treatment); however, mobility restriction may be reflecting not only the current moment but the history of the individual. It is important to bear that for cases on prophylaxis, the date of initiation is unknown, and mobility might have been influenced by the previous

Figure 4. Eligibility for surgery per severity of the disease and type of treatment.
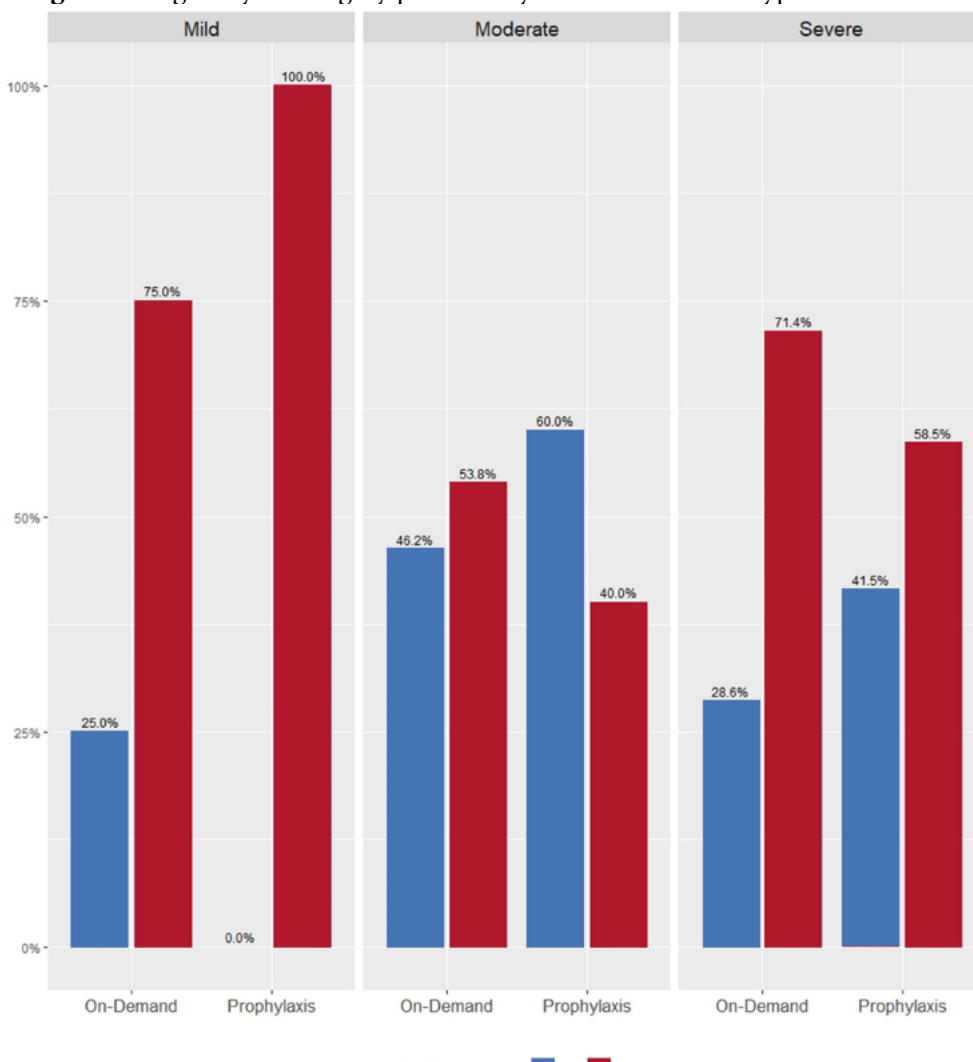
condition (i.e., before prophylaxis implementation). Also, there were considerable higher rates of ineligibility for surgery and ≥ 2 bleeding episodes in the same joint in the last 12 months for moderate and severe individuals in ranges of 28.6 - 60% and 10 - 42.9%, respectively; besides, ineligibility for surgery rate was higher for moderate individuals on prophylaxis (60%). Overall, the decision to perform surgery in patients with hemophilia requires careful consideration and planning and might be influenced by several factors, including the severity of the patient's hemophilia, their age, and their treatment history; a possible explanation for this might be that cases with a high ABR alone are considered to be at increased risk of bleeding complications during surgery, regardless of the severity and their treatment history[5].

Although there is no specific data on individuals with HA without inhibitors in Argentina, our findings coincide with a report of a multicenter, retrospective, real-world cohort of Argentinian HA individuals with inhibitors handled according to standard clinical practice published in 2017, that showed that most of them received treatment with bypassing agents either on-demand (56.5%) or as prophylaxis (18.8%) followed by Immune Tolerance Induction (ITI) (24.6%); being the main indication for long-term prophylaxis the failure of ITI (53.8%) and recurrent bleeding (46.2%). Additionally, it exhibited that even when the mean overall ABR was similar for the different strategies, the use of prophylactic treatment was associated with a significant decrease when compared with on-demand treatment[10].

It is interesting to note that in our sample, despite

having relatively adequate treatment regimes in terms of dosage and frequency of application, HA individuals without inhibitors still suffer from fairly frequent bleeding episodes, ≥ 2 bleeding episodes in the same joint, mild to severe mobility restrictions and ineligibility for surgery. Again, this trend was more evident for individuals with severe disease, both with and without prophylaxis, than those with mild or moderate disease, thus supporting the work of other clinical trials and real-world studies in this area[6,16-19]. In the context of our study, the term "adequate prophylaxis" refers to dosing regimens that encompass fixed doses based on weight and administration frequency. It's worth noting that the intricacies of individual cases conditions and pharmacokinetics are vital considerations for personalized care. While acknowledging their importance, our investigation focused on evaluating the specified dosing regimens; individual factors like baseline factor levels and pharmacokinetic adjustments were not within our scope, yet may be subject of further research.

Adherence in our sample was greater than 80% in just 55.2% of cases. These results reflect those of Kruse-Jarres et al., who found adherence to ≥80% of prescribed FVIII doses in 66.7% of individuals and a median ABR of 31.1 (IQR 19.8-51.6) and 5.0 (IQR 0.0-8.2) for cases receiving episodic and prophylactic treatment, respectively[6]. Perhaps the most compelling finding is that up to 41.5% of severe cases were reported to have an adherence of less than 80% and the previously mentioned higher ABR for severe cases. This might further provide support for the role of adherence and its effect on the aforementioned unmet needs within this population.

Insurance coverage is among the variables potentially related to access to health services that were evaluated in our study. It is interesting to mention that the PAMI provides coverage of health services almost exclusively to retired individuals and pensioners (i.e., primarily elderly individuals)[20]. The fact that the majority of severe individuals are affiliated with an OOSS has implications in terms of costs, given

that the resources of the OOSS *provincial*, and particularly, the funds for expensive and low-frequency treatments are not regulated nor supported by the Redistribution Solidarity Fund (*Fondo de Redistribución Solidaria* in Spanish), as is the case with the OOSS *Nacional*[21].

The generalizability of these results is subject to certain limitations. During the first period of data collection, we encountered challenges in gathering the entire sample size for our study. In order to address this limitation and ensure a complete dataset, we decided to conduct a second period of data collection. Splitting data collection into two time periods may introduce additional complexity to our study design, analysis, and interpretation; however, we believe that this approach was necessary to ensure a complete dataset and improve the quality and validity of our findings.

One of the more significant findings to emerge from this study is that despite appropriate doses and application intervals, there are still some unmet medical needs for Argentinian HA individuals without inhibitors; particularly for severe cases who showed a higher ABR, mobility restriction and consumption of FVIII. Novel therapeutic strategies and education on treatment-adherence and self-management of the disease would potentially reduce the number of bleeding events and consumption of FVIII products. Our study has established a foundational framework for future research endeavors, aimed at tackling unmet needs within the cohort of severe hemophilia A cases without inhibitors in Argentina. To enhance our comprehension, we recommend adopting analytical methodologies in upcoming studies, grounded in real-world evidence and on a centralized registry. This could encompass longitudinal studies to monitor evolving trends and incorporate control groups for more precise assessment of intervention effectiveness and causal links between interventions and outcomes, thus yielding essential insights for clinical decision-making. These efforts will aim to provide more definitive evidence essential to optimizing care strategies for this population.

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